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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO	CONFIRMATION NO
09/689,366	10/12/2000	Mike Rothe	T95-005-2	7997

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EXAMINER	
LEFFERS JR, GERALD G	
ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 04/01/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/689,366	ROTHE ET AL.	
	Examiner	Art Unit	
	Gerald G Leffers Jr.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 February 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *10 and 12-16* is/are pending in the application.

4a) Of the above claim(s) *14-16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10 and 12* is/are rejected.

7)☒ Claim(s) *13* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Receipt is acknowledged of an amendment, filed 2/19/03 as Paper No. 6, in which claim 11 was cancelled and in which several claims were amended (claims 12, 14, 16). Claims 10, 12-16 are pending in the instant application, with claims 14-16 withdrawn from consideration as being directed to nonelected inventions.

Election/Restrictions

Applicant's election of Group I (claims 10, 12 and 13) in Paper No. 6 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). In applicants' response in Paper No. 6, applicants have requested rejoinder of duly limited methods claims 13-16. Accordingly, upon the indication of an allowable product claim, the duly limited process claims dependent thereon will be rejoined (MPEP 821.04).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 10 and 12 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had

possession of the claimed invention. **This rejection is maintained for reasons f record in Paper No. 4, mailed 1/15/02 and repeated below.**

The rejected claims are directed towards an isolated human cellular inhibitor of apoptosis protein (c-IAP) comprising specific domains derived from the two c-IAP proteins of the invention. Claim 10 appears to be directed toward the 3rd BIR domain of c-IAP1 (amino acids 287-334 of SEQ ID NO: 2). Claim 12 appears to be directed towards hybrid proteins comprising at least 2 BIR domains derived from c-IAP1 or c-IAP2. The rejected claims encompass embodiments where the human c-IAP protein comprises other functional domains in addition to the BIR and RING finger domains described in the art or in the instant specification.

The specification describes the isolation of cDNAs encoding c-IAP1 and c-IAP2 by probing human cDNA libraries with a nucleic acid encoding a murine version of c-IAP. The human c-IAP proteins are described as having significant similarity to the mouse version of c-IAP (84% and 72%, respectively, for c-IAP1 and c-IAP2) and 73% homology to one another. Unlike the insect viral analogs, the mammalian IAPs (c-IAP1 and c-IAP2) are described as comprising 3 BIR domains rather than two such domains. However, unlike NAIP, another mammalian apoptosis inhibitor, the instant proteins comprise a RING finger motif similar to ones found in the insect viral analogs. Yeast two-hybrid analysis results are described which indicate that c-IAP1 and c-IAP2 interact with TRAF1 and TRAF2, two intracellular receptors for TNF. Deletion and hybrid experiments indicate that the BIR domains of c-IAP1 and c-IAP2 represent novel protein::protein interaction domains. The N-terminal domain of c-IAP1, comprising the 3 BIR motifs, is described as being sufficient to mediate interaction with the two

receptors. The RING finger domain does not appear to be essential for c-IAP interaction with the TRAF receptors.

It is clear from the description provided by the specification that c-IAP1 and c-IAP2 share several similar structural/functional domains with one another and with different apoptosis inhibitors known in the art. For example, it is noted that the first BIR domains from each of c-IAP1 and c-IAP2 (described by SEQ ID NOS: 1 and 2) differ at only 1 amino acid residue out of a total of 55 residues. However, it is also evident from reading the specification that there are significant differences between the previously known inhibitors of apoptosis and c-IAP1/c-IAP2, as well as between c-IAP1 and c-IAP2 (e.g. 27% non-homology between the two proteins). There is no structural/functional framework provided in the specification to allow one of skill in the art to envision exactly what a 3rd c-IAP protein obtained from humans would look like. For example, would such a third c-IAP protein necessarily comprise a RING-finger domain? Would a 3rd c-IAP protein comprising SEQ ID NO: 5 or SEQ ID NO: 6 necessarily comprise other BIR domains similar to the ones described herein (e.g. SEQ ID NOS: 7-10)? The specification teaches that it is the BIR domains that are likely to provide target specificity for c-IAP/target interaction. If additional human c-IAP proteins exist, it seems likely that they could be directed to other protein targets involved in mediating apoptosis. What would the BIR domains of such a protein look like? Again, the specification provides no basis to envision the primary amino acid sequence/structure of such a human c-IAP protein.

The prior art teaches that it is difficult to predict the structural/functional properties of a protein having a given primary amino acid sequence because the relationship between the sequence of a protein and its tertiary structure (in essence the structure which defines its

activity), is not well understood and is not predictable as evidenced by Berendsen (Science. 1998, Vol. 282, pages 642-643; see the entire document). This reference teaches that "Thus, one of the "grand challenges" of high-performance computer-predicting the structure of proteins-acquires much of the flavor of the Holy Grail quest of the legendary knights of King Arthur: It is extremely desirable to possess but extremely elusive to obtain." (Page 643, columns 1-2). The whole reference teaches about the unpredictability in the art concerning protein structure, and failures to make it predictable. Thus, as taught by Berendsen, the state of the art with regard to predicting the structural/functional characteristics of a protein having a given amino acid sequence is underdeveloped. Therefore, the prior art does not provide a structural/functional basis for one of skill in the art to envision additional embodiments of the claimed human c-IAP proteins comprising one or more of the recited domains of c-IAP1 and c-IAP2.

Given that the rejected claims encompass proteins comprising, or lacking, additional functional elements (e.g. BIR and RING-finger domains) to those described in the specification, and given that there is no structural/functional framework provided in the specification or prior art to envision additional embodiments of the claimed invention other than c-IAP1 and c-IAP2, one of skill in the art would not have been able to envision a representative number of embodiments of the claimed c-IAP proteins to describe the genus of such proteins. Therefore, one of skill in the art would have reasonably concluded applicants were not in possession of the claimed invention.

Response to Arguments

Applicant's arguments filed in Paper No. 6 have been fully considered but they are not persuasive. In Paper No. 6, claim 12 was amended to depend from claim 10. Applicants'

response essentially argues: 1) the sequence of SEQ ID NO: 2 defines a novel "third" BIR domain (SEQ ID NO: 9), 2) the specification teaches that the cIAP BIR domains represent novel protein-protein interaction domains and how multiple BIR domains can be mixed-and-matched in functional recombinant chimeras (e.g. page 12, lines 10-14 of the specification), 3) the specification shows in experimental detail how to screen for interactions of such BIR domain-containing proteins with proteins like TRAF (e.g. page 11, line 27-page 14, line 13), 4) discerning and practicing the claimed invention does not require invoking Holy Grails or King Arthur, 5) the invention does not relate to some hypothetical 3rd cIAP domain and does not require determining three dimensional molecular structures of anything, 6) the ability to recombine the domain into functional chimeric proteins is disclosed and 7) the claims are properly limited to a protein specifically comprising the novel interaction domain.

The rejected claims are drawn to proteins comprising cellular inhibitor of apoptosis activity where the protein comprises residues 287-334 of SEQ ID NO: 2 (claim 10). The rejected claims are limited in scope only in that they must comprise this sequence, or in the case of claim 12, a couple of additional BIR domains. The claims still comprise open claim language with regard to other protein sequences that may be present and which may be required in order to possess the recited c-IAP activity. As indicated in making the rejection, the instant specification does not provide a structural/functional basis for one of skill in the art to envision the additional protein domains that may be present in the proteins encompassed by the broadly claimed genus and which also retain the claimed functional activity. The passage of the instant specification indicated in the response merely indicate that domains within c-IAP1 and c-IAP2 may be switched to study c-IAP/TRAF interactions, without presenting actual data.

At no point did the examiner assert that one would have to invoke images from the legendary tales of King Arthur in order to determine applicants were in possession of the claimed proteins. However, with regard to envisioning the other functional domains that might be present in proteins encompassed by the broadly claimed genus of c-IAP proteins, it would be useful in the absence of a structural/functional framework provided by the prior art or instant specification to be able to reliably predict structural/functional characteristics of proteins encompassed by the claims from their primary sequence (e.g. for different combinations of BIR domains). The teachings of Berendsen were cited in making the rejection to indicate that such attempts to envision the three dimensional structural/functional characteristics of a protein are unreliable. Thus, there is no basis in the instant specification or prior art for one of skill in the art to envision a sufficient number of proteins encompassed by the rejected claims sufficient to describe the broadly claimed genus.

Conclusion

No claims are allowed. Claim 13 is objected to as being dependent upon a rejected claim, but would be allowable if rewritten in an independent form comprising each of the limitations of the claim upon which it is dependent.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gerald G Leffers Jr. whose telephone number is (703) 308-6232. The examiner can normally be reached on 9:30am-6:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached on (703) 305-1998. The fax phone numbers for the

organization where this application or proceeding is assigned are (703) 305-7939 for regular communications and (703) 305-7939 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Gerald G Leffers Jr.
Examiner
Art Unit 1636

Ggl
March 27, 2003